

JUN-16-05 02:22PM FROM-StoutUxaBuyanMullins

T-631 P.014/033 F-162

EXHIBIT B



Canadian Journal Journal canadien
of Surgery de chirurgie

April 1999

Avril 1999

The role of joint innervation in the pathogenesis of arthritis

Paul Salo, MD

Can J Surg 1999;42:91-100

[résumé]

From the McCaig Center for Joint Injury and Arthritis Research, Department of Surgery, University of Calgary, Calgary, Alta.

Accepted for publication May 7, 1998

Correspondence to: Dr. Paul Salo, Department of Surgery, The University of Calgary, 3330 Hospital Dr. NW, Calgary AB T2N 4N1

© 1999 Canadian Medical Association (full text / résumé)

Contents

- Abstract
- Résumé
- Introduction
- Articular neuroanatomy
- Neurons that innervate joints and their role in arthritis
- Future directions
- References

Abstract

Recently, an expanding body of knowledge has documented the nature and functions of receptors in joint tissues and their potential importance in preserving the smooth normal functioning of the motor-skeletal system and in amplifying the inflammatory response to joint injuries and diseases. This review summarizes the current knowledge of the anatomical and physiological substrates of these mechanisms. The distribution, morphologic and functional characteristics of joint receptors have been well described. In the past decade there has been a new appreciation of the major role played by sensory neurons in promoting regional inflammatory

responses, and many of the specific neuronal mechanisms and molecules that mediate these reflexes have been identified. This knowledge promises to significantly improve the selectivity and effectiveness of pharmacologic approaches to pain, trauma and regional inflammatory disorders.

Other investigations have revealed important contributions of joint receptors to motor function. These refer not to proprioception or the sense of limb position in space, but rather to a more sophisticated tailoring of muscle activity to increase joint stability and to protect joint structures from damaging loads. Whether a loss of these reflexes may play a role in the pathogenesis of osteoarthritis remains controversial. However, there is a growing consensus that a loss of these reflexes may contribute to the morbidity associated with disruption of the anterior cruciate ligament.

Synovial joints are sites of major interactions between the musculoskeletal and the nervous systems. Understanding the mechanisms that activate and control these interactions will certainly offer the opportunity to develop new, more effective treatments for patients with joint disorders.

[Contents]

Résumé

Un bloc croissant de connaissances a décrit récemment la nature et les fonctions des récepteurs des tissus des articulations et leur importance éventuelle dans la préservation du fonctionnement normal lisse du système moteur-squelettique et dans l'amplification de la réaction inflammatoire aux lésions et pathologies des articulations. On résume dans cette revue le savoir actuel sur les substrats anatomiques et physiologiques de ces mécanismes. Les caractéristiques relatives à la distribution, à la morphologie et au fonctionnement des récepteurs des articulations ont été bien décrites. Au cours de la dernière décennie, on a commencé à mieux comprendre le rôle important que jouent les neurones sensoriels dans la promotion des réactions inflammatoires régionales et l'on a identifié un grand nombre des molécules et des mécanismes neuronaux spécifiques qui provoquent ces réflexes. Ces connaissances amélioreront considérablement la sélectivité et l'efficacité des stratégies pharmacologiques de lutte contre la douleur, les traumatismes et les troubles inflammatoires régionaux.

D'autres investigations ont révélé que les récepteurs des articulations contribuent énormément à la fonction motrice. Ces contributions ont trait non pas à la proprioception, ou sensation de la position du membre dans l'espace, mais plutôt à

une réaction plus sophistiquée de l'activité musculaire qui vise à accroître la stabilité des articulations et à protéger les structures articulaires contre les charges dommageables. La question de savoir si les réflexes peuvent jouer un rôle dans la pathogénèse de l'ostéoarthrite suscite toujours la controverse. On reconnaît toutefois de plus en plus qu'une perte de ces réflexes peut contribuer à la morbidité associée à une rupture des ligaments croisés antérieurs.

Les articulations synoviales sont les sites d'interactions majeures entre les systèmes musculo-squelettique et nerveux. La compréhension des mécanismes qui activent et contrôlent ces interactions permettra certainement de mettre au point de nouveaux traitements plus efficaces pour les patients qui ont des troubles des articulations.

[Contents]

A primary function of the musculoskeletal system is to act as an effector system for the central nervous system, thereby providing an organism with the enormous advantage of an ability to purposefully manipulate the environment. It is sensible that a mechanism to monitor performance should be intrinsic to such a system, which is a teleologic explanation for the existence of specialized sensory receptors within muscle and joint tissues. Extensive information has accrued regarding the length- and tension-sensing functions of muscle spindle receptors and Golgi tendon receptors. In recent years an expanding body of knowledge has documented the nature and functions of receptors situated in joint tissues and their potential importance in preserving the normal functioning of the motor-skeletal system and in amplifying the inflammatory response to joint injuries and diseases.

Anyone who has experienced the pain and disability of a joint injury or inflammatory condition has first-hand knowledge of the potent reflex mechanisms mediated by joint receptors to protect an injured joint from further damage by activating the dynamic splinting and guarding effects of muscle spasm or the withdrawal response to pain. To what extent do protective neuronal reflexes actively participate in the generation and perpetuation of an inflammatory response? And are there other related reflexes that function routinely at an unconscious level to protect healthy joints from damage during normal activity?

[Contents]

Articular neuroanatomy

A majority of investigations of joint innervation have focused

on the knee joint. The vertebrate knee joint is supplied by 2 major articular nerves — the posterior articular nerve, which is a branch of the tibial nerve, and the medial articular nerve, which arises from the femoral or obturator nerve. Together these account for 80% to 90% of the neurons supplying the joint. Hilton proposed that joints receive some branches from all the nerves that supply muscles which traverse the joint; however, in the knee joint such accessory contributions seem to be variable, inconsistent and often absent.^{1,2}

All articular structures except articular cartilage are innervated.³ Joint nerves are composed of both myelinated and unmyelinated fibres. About 20% of the axons are myelinated. They contain large diameter mechanoreceptors, which are thickly myelinated and are rapid conductors, and smaller diameter, thinly myelinated nociceptors and mechanoreceptors. About 80% of the axons are unmyelinated, half are sympathetic fibres and the rest are sensory fibres.^{4,5}

Joint tissues contain a variety of sensory nerve endings, which can be broadly classified into 4 morphologic types (Table I). Three types are corpuscular mechanoreceptors and the fourth type, which is by far the most numerous, is the free nerve endings. Table I lists the types of receptors together with their typical locations in the cat knee and gives a simplified description of their functional characteristics. There seem to be some minor variations in receptor morphology across species, but these variations are unlikely to be responsible for significant functional differences.^{6,8} In general terms, these receptors respond to tension, pressure or noxious stimuli. There is likely some overlap of functions between receptor types; for example, some slowly conducting unmyelinated fibres are known to be responsive to mechanical stimuli.⁹

[Contents]

Neurons that innervate joints and their role in arthritis

Clinical observations indicate the existence of important interactions between the nervous system and joints involved by arthritis or injury. For example, rheumatoid arthritis typically occurs in a symmetrical pattern of joints, except in patients with focal neurologic disease, who may show sparing of paralysed or denervated joints.^{10,11} Reflex dystrophy syndrome is often accompanied by synovitis. A significant component of the disability accompanying disruption of the anterior cruciate ligament may be caused by the loss of proprioceptive mechanisms mediated by mechanoreceptors in

the ligament.^{6,12,13} Over the past decade there has been a remarkable increase in understanding the neural substrates of these clinical phenomena.

It is helpful to classify arthritis into 2 broad categories: inflammatory and degenerative. In inflammatory arthritis, the essential pathophysiology is the development of synovitis, with damage to joint soft-tissue constraints (joint capsule, ligaments and meniscal structures) and cartilage matrix occurring secondary to the actions of enzymes, cytokines, peptides, prostaglandins, free radicals and other mediators that are liberated by the inflammatory process. In degenerative arthritis, cartilage damage may result from excessive loading of normal cartilage or may reflect an intrinsic mechanical inadequacy of abnormal cartilage matrix that is unable to withstand normal loads. The role of joint-receptor-mediated reflexes in these 2 categories of arthritis will be considered.

Neuronal contributions to inflammatory arthritis

In 1937, Sir Thomas Lewis first postulated the existence of a "nocifensor system" of nerve fibres in skin, based primarily upon his observations of the cutaneous triple response: red line, flare and weal. This system, consisting of neurons coursing through the dorsal root ganglia, was thought to release mediators in the region of a noxious stimulus by the generation of antidromic impulses stimulated by the "axon reflex."¹⁴ The proposed function of these reflexes was the regionally selective promotion and amplification of the inflammatory response, the activation and facilitation of an appropriate local defence or a repair response after a noxious or damaging insult.

Over the past 20 years significant advances in our understanding of these reflex mechanisms have been made, together with the realization that they likely play an intrinsic role in all inflammatory conditions. Nowhere has this become more evident than in joints. Inflammatory arthritis induces profound changes in sensory neurons at their peripheral terminations, in their cell bodies in the dorsal root ganglia, in their spinal cord connections and even in the neurons that supply the contralateral joint.

Peripheral neurogenic mechanisms in inflammatory arthritis

Role of neuropeptides

About one-third of the unmyelinated free nerve endings in joints contain substance P or calcitonin gene-related peptide (CGRP), or both,^{15,16} peptides that are potent inflammatory

mediators. Substance P is a vasodilator, which increases capillary permeability, induces mast cell degranulation and is a potent leukocyte chemotactic agent.^{17,18} It is also mitogenic and chemotactic for endothelial cells and fibroblasts. CGRP is a potent vasodilator, a mitogen for endothelial cells and a potent inhibitor of insulin-mediated glycogen synthesis.¹⁹ Acting together, these neuron-derived peptides can significantly potentiate the inflammatory response, and they are released into the joint and peri-articular tissues during inflammatory arthritis.²⁰

Tissue injury increases the local expression of nerve growth factor by fibroblasts in response to tumour necrosis factor- α or interleukin-1 β .^{21,22} Levels of nerve growth factor in synovial fluid are significantly increased in patients with inflammatory arthritis.²³ Nerve growth factor is a trophic factor for mast cells, small diameter peptidergic neurons and sympathetic efferent neurons. Substance P and CGRP messenger RNA (mRNA) and peptide content in the dorsal root ganglia and dorsal horn of the spinal cord are increased dramatically after induction of experimental inflammatory arthritis as a result of increased expression of nerve growth factor in the damaged target tissue.^{17,24,29}

Two classes of peripheral nociceptor

About one-third of unmyelinated sensory fibres do not express substance P or CGRP. Recent investigations of these neurons have revealed enough characteristic differences to suggest that they should be considered in a separate functional class. They express a receptor for a different neurotrophic factor called glial-derived neurotrophic factor and also selectively express receptors for adenosine triphosphate that are not found on neuropeptide-containing neurons. Furthermore, this subgroup of unmyelinated sensory neurons exhibits a different pattern of axon termination in the dorsal horn of the spinal cord.^{30,31} The significance of these differences remains to be determined, but there is a clear indication that these different neuronal subtypes may mediate different types of pain and may therefore be selectively blocked by appropriate ligands.

Sensitization of joint afferent neurons during inflammation

Pain is one of the cardinal signs of arthritis and is usually associated with allodynia (pain to innocuous stimuli) and hyperalgesia (amplified pain to noxious stimuli). These perceptual changes are now known to reflect cellular and molecular changes in the cells of the dorsal root ganglia and the spinal cord. Allodynia and hyperalgesia come about

because of changes that originate almost exclusively in the smaller diameter thinly myelinated and unmyelinated populations of sensory fibres. These neurons exhibit enlargement of their receptive fields and decreased sensory thresholds to mechanical and noxious stimuli.⁴ Many neurons begin to fire spontaneously, and others fire at much higher rates in response to stimulation. Although many of the well-known inflammation-associated mediators (e.g., bradykinin, serotonin, prostaglandins) have been proposed as causes of or contributors to these changes in neuronal response properties, it was recently shown that almost all of the observed changes in the behaviour of these neurons may be induced by locally increased concentrations of nerve growth factor.³²³⁴

Role of autonomic fibres

Vasomotor reflexes become significantly altered during the inflammatory response to joint inflammation. Normal joint tissues have a relatively low baseline blood flow, which can be modulated by stimulation of sympathetic efferents or application of substance P and CGRP.^{35,36} These reflexes are abolished by adjuvant arthritis, which induces significant increases in joint blood flow that can no longer be altered by sympathetic stimulation or the application of neuropeptides.³⁷

Sympathetic fibres make a contribution to plasma extravasation. Increased tissue levels of bradykinin induce the release of serotonin (5-hydroxytryptamine) from mast cells and platelets. Serotonin mediates plasma extravasation from the synovial microcirculation by actions on 5-hydroxytryptamine-2A receptors that are found on sympathetic efferent terminals. It is thought that activation of the 5-hydroxytryptamine-2A receptor induces release of prostaglandins from the sympathetic terminal by a mechanism independent of action potentials or membrane depolarization. These effects are blocked by sympathectomy or selective antagonists at the 5-hydroxytryptamine-2A receptor.³⁸

Spinal reflexes regulate the regional inflammatory response

The severity of experimentally induced inflammatory arthritis of the rat knee joint can be significantly diminished by dorsal root transection, disconnecting the dorsal root ganglion from the spinal cord, but leaving *intact* the axons connected to the periphery.³⁹ This seminal observation indicates that a spinal cord circuit must mediate most of the release of the neuropeptides that amplify the inflammatory response.

According to this model, afferent volleys are carried by myelinated and unmyelinated nociceptive neurons into the spinal dorsal horn, where they synapse on second order neurons and interneurons.⁴⁰ The second order neurons or interneurons then activate other peptidergic neurons to antidromically conduct impulses back to the periphery, where substance P, CGRP and other neuromodulators are released. Although the precise spinal circuitry remains unknown, follow-up experiments have shown that these "dorsal root reflexes" utilize glutamate and gamma-aminobutyric acid (GABA) as transmitters and can be blocked by selective antagonists at the non-*N*-methyl-d-aspartate glutamate receptor and the GABA_A receptor.^{41,42}

Sensitization of intraspinal second order sensory neurons

Dorsal horn neurons of the spinal cord receiving input from joints may be classified into 2 types: nociceptive specific and wide dynamic range. Nociceptive-specific neurons respond only to noxious or damaging stimuli. Wide-dynamic-range neurons show a graded response to various stimuli, with very high outputs in response to noxious stimuli.⁹ Just as inflammation-associated allodynia and hyperalgesia arise from lowered thresholds of primary afferent neurons, these sensory disturbances also reflect significant increases in excitability of the both the wide-dynamic-range and nociceptive-specific types of second order sensory neurons in the spinal cord that show lowered thresholds, higher firing rates and sometimes spontaneous discharges. In recent years, the causes of these changes in excitability have been elucidated. Increased sensory traffic from the inflamed joint leads to localized increases in dorsal horn levels of glutamate, substance P and CGRP. Hyperexcitability of the second order neurons deep in the dorsal horn is principally caused by the actions of glutamate upon metabotropic glutamate receptors⁴³ and of GABA (presumably released from interneurons) upon the GABA_A receptor⁴¹ but is further augmented by the actions of intraspinal substance P and CGRP.^{44,45} Blockade of the metabotropic glutamate receptor or the GABA_A receptor can prevent the development of hyperexcitability of the second order sensory neurons in the spinal cord without affecting normal responses to innocuous and noxious stimuli.^{41,43}

Recent experiments have revealed that an experimental inflammatory arthritis can also increase substance P and CGRP production in the dorsal root ganglia and spinal cord *contralateral* to the inflamed joint and even induce a

symmetrical inflammation in the contralateral joint.^{46,47} These observations lend further support to the evidence that afferent and spinal mechanisms play a key role in the initiation and promotion of inflammation. These "contralateral effects" can be prevented by blockade of the "dorsal root reflexes" with appropriate antagonists to glutamate and GABA at the appropriate receptors.

Protective effects of joint afferent and efferent neurons

The inflammatory process plays important roles in defending against infection and in initiating repair mechanisms after injury. Our current understanding of the neurogenic contribution to inflammation fulfils the hypothetical role postulated by Sir Thomas Lewis for his "nocifensor" system. Furthermore, it has recently been shown that local immune responsiveness is increased by a glutamate-mediated spinal reflex.⁴⁸ The mechanism by which this occurs remains obscure. It also remains to be seen whether neurogenic inflammatory mechanisms have any significant influence on the outcome of tissue repair.

Clinical relevance

These recent findings are of broad clinical interest because they reawaken an interest in a previously under-appreciated and potentially significant capability of spinal cord and peripheral sensory neurons to regulate specific metabolic processes in a regionally selective manner. Targetting the upregulation of nerve growth factor in injured tissues or perhaps the specific neurotransmitter receptors on second order neurons in the spinal cord could realistically lead to the development of more effective drugs and treatment for trauma, postoperative inflammation and other forms of chronic arthritis in which inflammation contributes significantly to morbidity.

Neurologic factors in degenerative arthritis

Charcot's arthropathy

Charcot's arthropathy is a severe form of degenerative arthritis that occurs in patients with peripheral sensory neuropathy.^{49,52} Although Charcot believed the disease was caused by a loss of trophic substances derived from the nerves, leading to atrophy of the joint tissues, the views of Volkmann have subsequently dominated modern thinking.⁵¹ Volkmann and later Virchow argued that the loss of limb sensation compromised muscular function in the limb, leading to mechanical damage to the joint.⁵³ This became the consensus opinion of subsequent investigators. Although there has been considerable

speculation, the potential relationship of the pathogenic mechanisms of Charcot's arthropathy to the common forms of osteoarthritis remains controversial.^{12,13,54,55}

Osteoarthritis, aging and joint innervation

Osteoarthritis is one of commonest disabling conditions associated with aging. The prevalence of osteoarthritis correlates directly with age and shows an increase with every decade after the age of 25 years. Age is the highest risk factor for osteoarthritis,⁵⁶ and 27%, 34% and 44% of the population exhibit radiographic osteoarthritis of the knee in the seventh, eighth and ninth decades of life respectively.^{57,58} Yet the normal aging of articular cartilage and subchondral bone does not presage the pathological changes found in osteoarthritis,⁵⁶ and the underlying cause of the disorder remains unknown. As Brandt⁵⁹ suggested, the end stage of osteoarthritis represents "joint failure," but the primary defect may lie in cartilage, synovium, subchondral bone, ligament or the neuromuscular system. Indeed, it has been repeatedly suggested that a failure of protective neuromuscular reflexes could predispose people to osteoarthritis.^{60,62}

A number of investigations in humans have hinted that neural mechanisms may play an important protective role in normal joint function. For example, a study using metal-impregnation stains to examine biopsy specimens of human knee joint capsule and ligament obtained from elderly patients with osteoarthritis at the time of joint replacement surgery failed to detect any of the neural elements that could be found in newborn or adolescent tissue.⁶³ Another more recent study identified a group of seemingly normal subjects with very subtle deficiencies in motor coordination during walking gait, manifested by abnormal peak loading during the early stance phase.⁶² This subgroup of "normal" people might be particularly dependent on joint afferent systems to protect their joints from damaging loads or might even have a deficiency of joint afferent innervation. Taken together, these studies lend support to speculations that an age-related loss of joint sensory innervation could cause or accelerate the development of common human osteoarthritis.^{13,60,61}

Neurosensory function of ligaments

In recent years these speculations have been fuelled by experiments that found that simple knee joint denervation in dogs produced minimal to no cartilage degeneration at up to 16 months. However, if denervation was combined with

transection of the anterior cruciate ligament, then an extremely rapid and progressive knee joint degeneration did ensue.^{64,65}

These observations may be partially explained by electrophysiological studies in cats that have clearly established the existence of the neural circuitry necessary to allow joint afferent neurons to mediate functionally important motor reflexes that are appropriate to protect joint surfaces from damaging loads.^{12,13,54,6672} Briefly, ligament-associated mechanoreceptors have been found to have a major influence on muscle spindle activity by regulating gamma-motor neuron activation of the intrafusal muscle fibres. Stimulation of receptors in the cruciate ligaments, for example, increases gamma-motor neuron outflow, muscle spindle sensitivity and muscle tension in both the flexor and extensor muscles of the knee joint.^{69,70,73} The net effect is a reflex increase of limb stiffness in response to applied loads. This balancing of muscle activities acting across the joint increases joint stability, which could be expected to protect the joint surfaces from mechanical damage (Fig. 1).

Age-related loss of mouse knee joint innervation

Discussions about protective muscular reflexes mediated by joint receptors and their relationship to "idiopathic" degenerative arthritis are of less interest, however, unless there is a loss of joint innervation with aging. Age-related loss of neurons from the central nervous system is a well-established phenomenon but has not been widely documented in the peripheral nervous system. Experiments in our laboratory revealed that in mice, innervation of the knee joint can be accurately and consistently quantified by retrograde tracing with the fluorescent dye Fluoro-Gold (Fluorochrome, Inc., Inglewood, Colo.). When this technique was used in C57BL/6 mice of different ages, a 60% loss of joint afferent neurons over the life span of the mouse was found.⁷⁴ Most of the loss occurs in the first 6 months of the mouse's 2-year mean life span and precedes the onset of degenerative arthritis, which has been reported to occur in this strain of mice.^{75,76} Rats are genetically closely related to mice but are rarely afflicted by degenerative arthritis. Interestingly, in experiments using Fluoro-Gold labelling of joint innervation in aging rats I found no losses of joint innervation with aging (unpublished data).

Joint receptor function in humans

Because few investigators studying human specimens have attempted to accurately quantify innervation of the knee joint, it remains unknown whether similar losses can and do occur in humans. However, in a series of studies some have attempted

to approach this question indirectly by examining proprioceptive function in the hip and knee joint of awake human subjects. These studies did show some impairment of joint position sense with aging and after ligament injury or joint replacement injury.⁷⁷⁸⁰ However, the relationship of a diminution of the conscious perception of joint position and movement to the type of protective muscular reflexes I have described is questionable at best. It is now clear that the conscious perception of joint position is mediated almost exclusively by muscle spindle receptors.⁸¹ The perception of joint or limb position in space is an important and useful sensory function, but it is not the same as the detection and modulation of joint loads, which is an unconscious, reflex motor function. A more useful (although more technically challenging) study of the function of joint receptors and the consequences of their loss would attempt to quantify muscle activities during load-bearing activity. A loss of joint receptor input would be expected to result in a disturbance of the normal balance of muscle forces across the knee joint. Such a study has been done. In 2 recent papers^{73,82} it was reported that in a group of patients with chronic anterior cruciate ligament injury there were measurable changes in motor function. Patients and uninjured control subjects were tested while performing isokinetic resisted knee flexion and extension. Patients generated significantly lower electromyographic activity and muscle force in the hamstring muscles when compared with normal subjects performing the same exercise or when compared with the patient's contralateral uninjured limb. Of particular note is that surgical reconstruction of the anterior cruciate ligament did not change these observed differences.^{73,82} These observations are consistent with our current view of ligament-associated mechanoreceptor function derived from the animal laboratory investigations already described. They lend support to the contention that a major element of ligament function is neurosensory and would appear to indicate that the loss of this function is not adequately addressed by the current standard surgical techniques of ligament reconstruction.

Clinical relevance

A cautious interpretation of the currently available data would suggest that if there is an age-related loss of joint innervation in humans, it could be a contributing factor in the pathogenesis of osteoarthritis. Such a loss would likely be of greater significance in association with some type of injury to the joint. In addition, it is wise to recall that the pathogenesis of osteoarthritis is likely multifactorial. Many extrinsic factors such as body mass, activity levels, limb alignment and

soft-tissue constraint are also important determinants of the loading history of articular cartilage surfaces, surfaces that almost certainly vary in their tolerance of load, injury and wear.

Current treatments for anterior cruciate ligament deficiency do not address the potentially important neurosensory properties of the native ligament. This may prove to have a significant impact on the ultimate outcome in these patients.

[Contents]

Future directions

The growth of knowledge of the fundamental workings of the nervous system has been explosive. As our knowledge of the role of neural systems and mechanisms in articular health and disease continues to expand, our capability to intervene effectively will also improve. The recent advances in understanding of afferent and spinal cord mechanisms clearly outline the potential for the development of selective drug therapies that could greatly reduce the pain and inflammation of arthritis or joint injury without interfering with normal sensory functions or tissue repair. If age-related loss of joint innervation does prove to be a contributor to the pathogenesis of osteoarthritis, then our approaches to prevention and treatment would understandably be radically altered. Similarly, increased recognition of the role of ligaments' sensory properties could lead to changes in operative techniques or to the development of methods to improve the survival and regeneration of damaged receptors.

Thanks to Dr. K.W. Marshall for assistance with the illustration and to Dr. R.D. Inman for helpful comments.

Supported by MRC grant MT13161.

[Contents]



Send a letter to the editor
Envoyez une lettre à la rédaction

References

1. Gardner E. The innervation of the knee joint. *Anat Rec* 1948;101:109-30.
2. Freeman MAR, Wyke B. The innervation of the knee joint. An anatomical and histological study in the cat. *J Anat* 1967;101:505-32.
3. Theriault E, Marshall KW, Homonko DA. Maintained

- peptidergic innervation of the knee joint in an animal model of antigen-induced arthritis. *Regul Pept* 1993;46:204-7.
4. Schaible HG, Schmidt RF. Activation of group III and group IV sensory units in medial articular nerve by local mechanical stimulation of the knee joint. *J Neurophysiol* 1983;49:35-44.
 5. Craig AD, Heppelmann B, Schaible HG. The projection of the medial and posterior articular nerves of the cat's knee to the spinal cord. *J Comp Neurol* 1988;276:279-88.
 6. Yahia LH, Newman N. Mechanoreceptors in the canine anterior cruciate ligaments. *Anat Anz* 1991;173:233-8.
 7. Schenk I, Spaeth A, Halata Z. The structure of sensory nerve endings in the knee joint capsule of the dog. *Ann Anat* 1996;178:515-21.
 8. Backenköhler U, Strasmann TJ, Halata Z. Topography of mechanoreceptors in the shoulder joint region — a computer-aided 3D reconstruction in the laboratory mouse. *Anat Rec* 1997;248:433-41.
 9. Schaible H-G, Grubb BD. Afferent and spinal mechanisms of joint pain. *Pain* 1993;55:5-54.
 10. Thompson M, Bywaters EG. Unilateral rheumatoid arthritis following hemiplegia. *Ann Rheum Dis* 1962;21:370-7.
 11. Glick EN. Asymmetrical rheumatoid arthritis after poliomyelitis. *BMJ* 1967;3(556):26-8.
 12. Johansson H, Sjölander P, Sojka P. A sensory role for the cruciate ligaments. *Clin Orthop* 1991;268:161-78.
 13. Marshall KW, Tatton WG. Joint receptors modulate short and long latency muscle responses in the awake cat. *Exp Brain Res* 1990;83(1):137-50.
 14. Lewis T. The nocifensor system of nerves and its reactions. *BMJ* 1937;194:431-5.
 15. Hanesch U, Heppelmann B, Schmidt RF. Substance P- and calcitonin gene-related peptide immunoreactivity in primary afferent neurons of the cat's knee joint. *Neuroscience* 1991;45(1):185-93.
 16. Salo PT, Theriault ET. Number, distribution, and neuropeptide content of rat knee joint afferents. *J Anat* 1997;190:515-22.
 17. Lembeck F, Donnerer J, Colpaert FC. Increase in substance P in primary afferent nerves during chronic pain. *Neuropeptides* 1981;1:175-80.
 18. Levine JD, Clark R, Devor M, Helms C, Moskowitz MA, Basbaum AI. Intraneuronal substance P contributes to the severity of experimental arthritis. *Science* 1984;226(4674):547-9.
 19. Lundberg JM. Pharmacology of cotransmission in the autonomic nervous system: integrative aspects on

- amines, neuropeptides, adenosine triphosphate, amino acids and nitric oxide [review]. *Pharmacol Rev* 1996;48(1):113-78.
20. Yaksh TL. Substance P release from knee joint afferent terminals modulation by opioids. *Brain Res* 1988;458:319-24.
 21. Hattori A, Tanaka E, Murase K, Ishida N, Chatani Y, Tsujimoto M, et al. Tumor necrosis factor stimulates the synthesis and secretion of biologically active nerve growth factor in non-neuronal cells. *J Biol Chem* 1993;268(4):2577-82.
 22. Safieh-Garabedian B, Poole S, Allchorne A, Winter J, Woolf CJ. Contribution of interleukin-1 beta to the inflammation-induced increase in nerve growth factor levels and inflammatory hyperalgesia. *Br J Pharmacol* 1995;115(7):1265-75.
 23. Aloe L, Tuveri MA, Carcassi U, Levi-Montalcini R. Nerve growth factor in the synovial fluid of patients with chronic arthritis. *Arthritis Rheum* 1992;35:351-66.
 24. Oku R, Sato M, Tagaki H. Release of substance P from the spinal dorsal horn is enhanced in polyarthritic rats. *Neurosci Lett* 1987;74:315-9.
 25. Sluka KA, Dougherty PM, Sorkin LS, Willis WD. Neural changes in acute arthritis in monkeys. III. Changes in substance P, calcitonin gene-related peptide, and glutamate in the dorsal horn of the spinal cord. *Brain Res Rev* 1992;17:29-38.
 26. Smith GD, Harmer AJ, McQueen DS, Seckl JR. Increase in substance P and CGRP, but not somatostatin content of innervating dorsal root ganglia in adjuvant monoarthritis in the rat. *Neurosci Lett* 1992;137:257-60.
 27. Lewin GR, Mendell LM. Nerve growth factor and nociception. *Trends Neurosci* 1993;16:353-9.
 28. Garrett NE, Kidd BL, Cruwys SC, Tomlinson DR. Changes in preprotachykinin mRNA expression and substance P levels in dorsal root ganglia of monoarthritic rats: comparison with changes in synovial substance P levels. *Brain Res* 1995;675:203-7.
 29. Hanesch U, Heppelmann B, Schmidt RF. Quantification of cat's articular afferents containing calcitonin gene-related peptide or substance P innervating normal and acutely inflamed knee joints. *Neurosci Lett* 1997;233:105-8.
 30. Molliver DC, Radeke MJ, Feinstein SC, Snider WD. Presence or absence of TrkA protein distinguishes subsets of small sensory neurons with unique cytochemical characteristics and dorsal horn projections. *J Comp Neurol* 1995;361:404-16.
 31. Snider WD, McMahon SD. Tackling pain at the source: new ideas about nociceptors. *Neuron* 1998;20:629-32.

32. Gentle MJ, Thorp BH. Sensory properties of ankle joint capsule mechanoreceptors in acute monoarthritic chickens. *Pain* 1994;57:361-74.
33. Lewin GR, Rueff A, Mendell LM. Peripheral and central mechanisms of NGF-induced hyperalgesia. *Eur J Neurosci* 1994;6:1903-12.
34. Ma Q-P, Woolf CJ. The progressive tactile hyperalgesia induced by peripheral inflammation is nerve growth factor dependent. *Neuroreport* 1997;8(4):807-10.
35. Karimian SM, McDougall JJ, Ferrell WR. Neuropeptidergic and autonomic control of the vasculature of the rat knee revealed by laser Doppler perfusion imaging. *Exp Physiol* 1995;80:341-8.
36. Ferrell WR, McDougall JJ, Bray RC. Spatial heterogeneity of the effects of calcitonin gene-related peptide (CGRP) on the microvasculature of ligaments in the rabbit knee joint. *Br J Pharmacol* 1997;121:1397-405.
37. McDougall JJ, Karimian SM, Ferrell WR. Prolonged alteration of vasoconstrictor and vasodilator responses in rat knee joints by adjuvant monoarthritis. *Exp Physiol* 1995;80:349-57.
38. Pierce PA, Xie G-X, Peroutka SJ, Green PG, Levine JD. 5-hydroxytryptamine-induced synovial plasma extravasation is mediated via 5-hydroxytryptamine2A receptors on sympathetic efferent terminals. *J Pharmacol Exp Ther* 1995;275(1):502-8.
39. Rees H, Westlund KN, Willis WD. Do dorsal root reflexes augment peripheral inflammation? *Neuroreport* 1994;5:821-4.
40. Wall PD, Lidierth M. Five sources of a dorsal root potential: their interactions and origins in the superficial dorsal horn. *J Neurophysiol* 1997;78:860-71.
41. Sluka KA, Willis WD, Westlund KN. Inflammation-induced release of excitatory amino acids is prevented by spinal administration of a GABA-A but not by a GABA-B receptor antagonist in rats. *J Pharmacol Exp Ther* 1994;271:76-82.
42. Rees H, Sluka KA, Westlund KN, Willis WD. The role of glutamate and GABA receptors in the generation of dorsal root reflexes by acute arthritis in the anaesthetized rat. *J Physiol* 1995;484:437-45.
43. Neugebauer V, Lucke T, Schaible HG. Requirement of metabotropic glutamate receptors for the generation of inflammation-evoked hyperexcitability in rat spinal cord neurons. *Eur J Neurosci* 1994;6(7):1179-86.
44. Neugebauer V, Weireter F, Schaible H-G. Involvement of substance P and neurokinin-1 receptors in the hyperexcitability of dorsal horn neurons during the development of acute arthritis in rat's knee joint. *J*

- Neurophysiol* 1995;73:1574-83.
45. Neugebauer V, Rumenapp P, Schaible H-G. Calcitonin gene-related peptide is involved in the spinal processing of mechanosensory input from the rat's knee joint and in the generation and maintenance of hyperexcitability of dorsal horn cells during development of acute inflammation. *Neuroscience* 1996;71:1095-109.
 46. Traub RJ, Solodkin A, Gebhart GF. NADPH-diaphorase histochemistry provides evidence for a bilateral, somatotopically inappropriate response to unilateral hindpaw inflammation in the rat. *Brain Res* 1994;647:113-23.
 47. Donaldson LF, McQueen DS, Seckl JR. Neuropeptide gene expression and capsaicin-sensitive primary afferents: maintenance and spread of adjuvant arthritis in the rat. *J Physiol* 1995;486:473-82.
 48. Herzberg U, Murtaugh MP, Carroll D, Beitz AJ. Spinal cord NMDA receptors modulate peripheral immune responses and spinal cord c-fos expression after immune challenge in rats subjected to unilateral mononeuropathy. *J Neurosci* 1996;16:730-43.
 49. Charcot JM. Sur quelques arthropathies qui paraissent d'épendre d'une lésion du cerveau ou de la moelle épinière. *Arch Physiol Norm Pathol* 1868;1:161.
 50. Johnson JTH. Neuropathic fractures and joint injuries: pathogenesis and rationale of prevention and treatment. *J Bone Joint Surg [Am]* 1967;49:1-30.
 51. Resnick D. Neuroarthropathy. In: Resnick D, Niwayama G, editors. *Diagnosis of bone and joint disorders*. Philadelphia: WB Saunders; 1988. p. 3154-85.
 52. Ellman MH. Neuropathic joint disease (Charcot joints). In: McCarty DJ, editor. *Arthritis and allied conditions*. Philadelphia: Lea & Febiger; 1989. p. 1255-72.
 53. Delano P. The pathogenesis of Charcot's joint. *AJR* 1946;56:189-200.
 54. Johansson H, Sjolander P, Sojka P. Receptors in the knee joint ligaments and their role in the biomechanics of the joint. *Crit Rev Biomed Eng* 1991;18(5):341-68.
 55. O'Connor BL, Brandt KD. Neurogenic factors in the etiopathogenesis of osteoarthritis. *Rheum Dis Clin North Am* 1993;19:581-605.
 56. Brandt KD, Fife RS. Ageing in relation to the pathogenesis of osteoarthritis. *Clin Rheum Dis* 1986;12(2):117-30.
 57. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987;30(8):914-8.
 58. *Basic data on arthritis of the knee, hip and sacroiliac joints in adults ages 25-74 years, United States,*

- 1971/1975. Washington: National Center for Health Statistics; 1979.
59. Brandt KD. The pathogenesis of osteoarthritis. *Eular Bull* 1992;21:75-81.
 60. Farfan HF. On the nature of arthritis. *J Rheumatol* 1983;10(Suppl 9):103-4.
 61. Cooke TDV. Pathogenetic mechanisms in polyarticular osteoarthritis [review]. *Clin Rheum Dis* 1985;11(2):203-38.
 62. Radin EL, Yang KH, Riegger K, Kish VL, O'Connor JJ. Relationship between lower limb dynamics and knee joint pain. *J Orthop Res* 1991;9:398-405.
 63. Schultz RA, Miller DC, Kerr CS, Micheli L. Mechanoreceptors in human cruciate ligaments. A histological study. *J Bone Joint Surg [Am]* 1984;66:1072-6.
 64. O'Connor BL, Palmoski MJ, Brandt KD. Neurogenic acceleration of degenerative joint lesions. *J Bone Joint Surg [Am]* 1985;67:562-72.
 65. O'Connor BL, Visco DM, Brandt KD, Myers SL, Kalasinski LA. Neurogenic acceleration of osteoarthritis. *J Bone Joint Surg [Am]* 1992;74:367-76.
 66. Johansson H, Sjolander P, Sojka P. Actions on gamma motoneurons elicited by electrical stimulation of joint afferent fibres in the hind limb of the cat. *J Physiol* 1986;375:137-52.
 67. Johansson H, Sjölander P, Sojka P. Fusimotor reflexes in triceps surae muscle elicited by natural and electrical stimulation of joint afferents. *Neuro-Orthop* 1988;6:667-80.
 68. Johansson H, Sjölander P, Sojka P, Wadell I. Reflex actions on the gamma-muscle-spindle systems of muscles acting at the knee joint elicited by stretch of the posterior cruciate ligament. *Neuro-Orthop* 1989;8:9-21.
 69. Sojka P, Johansson H, Sjolander P, Lorentzon R, Djupsjöbacka M. Fusimotor neurones can be reflexly influenced by activity in receptor afferents from the posterior cruciate ligament. *Brain Res* 1989;483:177-83.
 70. Johansson H, Sjölander P, Sojka P. Activity in receptor afferents from the anterior cruciate ligament evokes reflex effects on fusimotor neurones. *Neurosci Res* 1990;8:54-9.
 71. Sojka P, Sjolander P, Johansson H, Djupsjöbacka M. Influence from stretch-sensitive receptors in the collateral ligaments of the knee joint on the gamma-muscle-spindle systems of flexor and extensor muscles. *Neurosci Res* 1991;11:55-62.
 72. Buchanan TS, Kim AW, Lloyd DG. Selective muscle activation following rapid varus/valgus perturbations at the knee. *Med Sci Sport Exerc* 1996;28:870-6.

73. Osterling LR, Caster BL, James CR. Contralateral hamstring (biceps femoris) coactivation patterns and anterior cruciate ligament dysfunction. *Med Sci Sports Exerc* 1995;27:805-8.
74. Salo PT, Tatton WG. Age-related loss of knee joint afferents in mice. *J Neurosci Res* 1993;35:664-77.
75. Maier I, Wilhelm G. Osteoarthritis-like disease in mice: effects of anti-arthrotic and anti-rheumatic agents. In: Lott DJ, Jasani MK, Birdwood GFB, editors. *Studies in osteoarthritis: pathogenesis, intervention and assessment*. Chichester (NY): John Wiley and Sons; 1987. p. 75-83.
76. Wilhelm G, Maier R. Observations on the influence of weight-bearing stress and movement on the joints of mice predisposed to osteo-arthritis. *Aktuelle Rheumatol* 1987;12:161-7.
77. Barrack RL, Skinner HB, Cook SD, Haddad RJ. Effect of articular disease and total knee arthroplasty on knee joint-position sense. *J Neurophysiol* 1983;50:684-7.
78. Barrack RL, Skinner HB, Buckley SL. Proprioception in the anterior cruciate deficient knee. *Am J Sports Med* 1989;17:1-6.
79. Timoney JM, Inman WS, Quesada PM, Sharkey PF, Barrack RL, Skinner HB, et al. Return of normal gait patterns after anterior cruciate ligament reconstruction. *Am J Sports Med* 1993;21(6):887-9.
80. Simmons S, Lephart S, Rubash H, Borsa P, Barrack RL. Proprioception following total knee arthroplasty with and without the posterior cruciate ligament. *J Arthroplasty* 1996;11:763-8.
81. Proske U, Schaible H-G, Schmidt RF. Joint receptors and kinaesthesia. *Exp Brain Res* 1988;72:219-24.
82. Osterling LR, James CR, Bercades DT. Eccentric knee flexor torque following anterior cruciate ligament surgery. *Med Sci Sports Exerc* 1996;28:1229-34.